REMARKS

Claims 1-73 are pending and under consideration. Claims 7-9, 14, 51 and 59 have been amended. No claims have been added or canceled. Applicant notes with appreciation that Claims 2-3 are indicated as being allowed and that Claim 6 would be allowable if rewritten in independent form. The various substantive rejections of the remaining claims, as well as the other defects noted by the Patent Office, are addressed in detail below in the order raised in the Patent Office.

1. THE AMENDMENTS OF THE SPECIFICATION

The specification has been amended to change the sequence identifier of polynucleotide SC6 described at Col. 49, line 41 from SEQ ID NO:64 to SEQ ID NO:74 in order to conform the specification with the identifiers assigned in the Substitute Sequence Listing. No new matter is introduced into the application by virtue of this amendment.

2. THE AMENDMENTS OF THE CLAIMS

Claim 7 has been amended to include a final step of detecting or quantifying the released nucleotide or polynucleotide. The amendment is supported by the original patent at Col. 11, lines 11-7 and Col. 43, lines 12. The amendments of Claims 8 and 9 merely conform their language with the language of amended Claim 7. Their scope is unchanged.

Line 1 of Claim 14 has been amended to delete "is comprises" in favor of "comprises" to correct the defect noted by the Patent Office at paragraph 11 of the Office Action. This amendment merely corrects a typographical error, leaving the scope of the claim unchanged.

Claims 51 and 59 have been amended to correct obvious errors in antecedent basis, leaving their scope unchanged. The amendments are supported by FIGS. 11 & 12.

The amendments of Claims 7-9, 14, 51 and 59 do not introduce new matter into the reissue application. Entry into the application is therefore kindly requested.

3. SURRENDERING OF ORIGINAL PATENT

The Patent Office notes the instant reissue application was filed without an offer to surrender the original patent. Applicant submits that an offer to surrender the original patent is already of record– it was included with Applicant's response to the Notice to File Missing

Parts of Application mailed 24 July 2000. For the convenience of the Patent Office, a copy of the offer to surrender is attached hereto as Exhibit B.

4. DRAWINGS

The Patent Office alleges the drawings submitted with the instant application do not meet the requirements of 37 CFR § 1.84 and suggests deleting the word "new" from the figure captions. Applicant believes the drawings are correct as filed. Figures 1-7 were copied from the original patent and have not been amended (see 37 CFR § 1.173 (a)(2)). Thus, these figure captions do not include the expression "New." Figures 8-18 were added to the instant reissue application with the Preliminary Amendment filed concurrently with the application. Pursuant to 37 CFR § 1.173(b)(3), any figure added to a reissue application must be identified as "New." Since Figures 8-18 were newly added to the reissue application, it is believed that the designation of "New" in each of their respective captions is proper.

5. SEQUENCE LISTING

Pursuant to the provisions of 37 CFR §§ 1.821 through 1.825, Applicant submits herewith paper and computer-readable copies of a Substitute Sequence Listing identifying the sequences of the various polynucleotides and polypeptides described in the application. In the Substitute Sequence Listing, SEQ ID NOS:1-63 correspond to SEQ ID NOS:1-63 of the original patent; SEQ ID NOS:64-73 set for the sequences of the polynucleotides described in Applicants Preliminary Amendment and SEQ ID NO:74 sets for the sequence of polynucleotide SC6 described at Col. 49, line 41 of the original patent. The paper and computer-readable copies of the Substitute Sequence Listing are the same and do not introduce new matter into the application. Accordingly, please replace any paper and computer-readable sequence listings of record with the enclosed Substitute Sequence Listing.

6. NEW MATTER AND REJECTION OF CLAIMS 7-73 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 7-73 stand rejected under 35 U.S.C. § 251 as being based upon new matter added to the patent for which reissue is sought. The Patent Office considers the following subject matter, which was added to the instant reissue application by way of a Preliminary

Amendment filed concurrently with the application, "new:" FIGS. 8-18; the legends to FIGS. 8-18; SEQ ID NOS:64-73; and text of Example 4. Claims 7-73 are further rejected under 35 U.S.C. § 112, first paragraph, for lack of written description support. Applicant traverses the rejections.

Regarding the rejection based upon new matter, the Patent Office suggests that the originally filed application did not effectively incorporate by reference the subject matter added by amendment. In particular, in the paragraph bridging pages 4-5, the Office Action states: mere reference to another application, patent or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. § 112, first paragraph (citing *In re de Seversky*, 177 USPQ 144 (CCPA 1973)).

It is well settled that amendments that replace subject matter incorporated into an application by reference with the actual text and figures of the incorporated document do not constitute new matter. *See, e.g.*, MPEP § 2163.07(b). Thus, amendments inserting into an application text and/or figures from a document incorporated therein do not constitute new matter when: (i) subject matter from the document was effectively incorporated into the disclosure of the application by reference to the document; and (ii) the text and figures of the document inserted into the application by amendment correspond to the subject matter of the document that was incorporated by reference thereto.

As pointed out by Applicant in its Preliminary Amendment submitted concurrently with the instant reissue application, the material added by amendment corresponds to the actual text and figures of subject matter from Harrington & Lieber, 1995, *J. Biol. Chem.* 270:4503 ("Harrington & Lieber"). The question, then, is whether the added material was effectively incorporated by reference into the original patent application.

There can be no doubt that the added material was properly and effectively incorporated into the original patent by reference and therefore constitutes a part of the original patent disclosure. The instant original patent does not make "mere reference" to another application, patent or publication. It makes *specific reference* to *specific subject matter*– flap substrates, cleavage reactions and binding reactions– and identifies where it may be found:

> DNA flap substrates, cleavage and binding reactions and the like *are practiced with reference to* the Experimental Examples and . . . Harrington & Lieber (1995) *J. Biol. Chem.* 270:4503.

'283 Patent, Col. 39, line 65 through Col. 40, line 3, emphasis supplied). Such specific references have long been considered effective to incorporate the referenced subject matter into the disclosure of the referencing application. *See, e.g, In re Voss*, 194 USPQ 267 (CCPA 1977); *In re Hughes*, 193 USPQ 141 (CCPA 1977); *In re Fouche*, 169 USPQ 429 (CCPA 1971).

In re Voss is illustrative. In *In re Voss*, the application was a continuation-in-part of an earlier-filed parent application. The parent application referenced an issued patent for its discussion of certain ceramic materials. The issue was whether the referenced subject matter was incorporated into, and therefore a part of, the disclosure of the parent application. The specific "referencing" language read as follows:

> Reference is made to United States Patent No. 2,920,971, granted to S.D. Stookey, for a general discussion of glass-ceramic materials and their production.

In re Voss, 194 USPQ at 269. The court found this language effective to incorporate the referenced subject matter into the disclosure of the parent application:

> Rather than include in his application a detailed discussion of how to prepare such known starting materials, [Voss], for economy, referred the skilled artisan to Stookey '971. *It is clear that [Voss] intended the "discussion of glass-ceramic materials and their production" in Stookey '971 to become part of his parent application. The board erred in finding otherwise.*

In re Voss, 194 USPQ at 271 (citations omitted; emphasis supplied).[1/]

The cited *In re de Seversky* case is inapposite. In that case, de Seversky sought to antedate a prior art reference by showing that he was entitled to the filing date of an earlier-filed parent application. The parent application was a continuation-in-part ("CIP") of an

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[1/] Similar language was held to constitute a proper incorporation by reference in *In re Hughes*, 193 USPQ 141, 143 (CCPA 1977) ("Reference is made to application Serial No. 131,108 for complete descriptions of methods for preparing aqueous polymeric dispersions applicable in the hereinafter described invention."). Even less precise language was held to constitute a proper incorporation by reference in *In re Fouche*, 169 USPQ 429, 169 (CCPA 1971) (The compound can be "prepared as described in Example 1 of our application No. —.").

earlier-filed grandparent application. de Seversky admitted that the parent application did not disclose the subject matter necessary to support the claims. However, he urged that this was cured by virtue of the chain of priority, because the grandparent application did disclose the subject matter. According to de Seversky, since the parent application was a CIP of the grandparent application, the grandparent's disclosure was *ipso facto* incorporated by reference into the disclosure of the parent application.

In this context, the court found the CIP "referencing" language insufficient to incorporate any part of the disclosure of the grandparent application into the parent application. The court explained:

> To be sure, the statement that an application is a continuation-in-part, or a continuation, or a division, or in part a continuation of another application is in a broad sense a "reference" to the earlier application, but a mere *reference* to another application, or patent, or publication is not an *incorporation* of anything therein into the application containing such reference for the purposes of the disclosure required by 35 U.S.C. § 112.
>
> * * *
>
> As the expression itself implies, the purpose of "incorporation by reference" is to make one document become a part of another document by referring to the former in the latter *in such a manner* that is apparent that the cited document is part of the referencing document as if it were fully set out therein.
>
> We held in *Lund* [153 USPQ 625 (CCPA 1967)] that the mere statement that an application is a "continuation-in-part" does not do that.

In re de Seversky, 177 USPQ at 146-147 (emphases in original).

The holding of *In re de Seversky*– that a mere statement in an application "referencing" it as a continuation-in-part of a parent application does not serve to incorporate any part of the parent application into the disclosure of the referencing application– is irrelevant to the instant case. The instant application is not a continuation, divisional or continuation-in-part of any earlier-filed applications.

Applicant's referencing language is virtually identical to that of *In re Voss*. It clearly identifies the subject matter incorporated (DNA flap substrates, cleavage reactions and binding reactions) and where it is found (the Harrington & Lieber article, among others).

From this, it is clear that Applicant intended the DNA flap substrates, cleavage reactions and binding reactions described in the referenced Harrington & Lieber article to become a part of the original patent disclosure.[2/] Accordingly Applicant's referencing statement is effective to incorporate the referenced subject matter into the disclosure of the original patent.[3/]

Moreover, the subject matter added by amendment corresponds to, and merely replaces, the incorporated material with the actual text and figures of the incorporated document. Specifically, the various DNA flap structures illustrated in instant FIGS. 8-12 correspond to the various incorporated DNA flap structures illustrated and described in the Harrington & Lieber article at FIGS. 1, 3, 4, and 5. Instant FIGS. 13-18, which illustrate the results of the incorporated binding and cleavage reactions, correspond to FIGS. 1-6, respectively, of the Harrington & Lieber article. The instant FIG. legends correspond to the legends of their respective figures of the Harrington & Lieber article. SEQ ID NOS:64-73 set forth the nucleotide sequences of the polynucleotides comprising the various illustrated DNA flap and other structures assessed in the binding and cleavage reactions. New Example 4 corresponds to the portions of the Harrington & Lieber article that describe the incorporated binding and cleavage reactions.

A table detailing how the material incorporated by reference from the Harrington & Lieber article corresponds to the subject matter added by amendment is provided below:

[2/] *See also*, MPEP § 2163.07(b) ("The information incorporated is as much a part of the application as filed as if the text was repeated in the application.").

[3/] The entire Harrington & Lieber article was also specifically incorporated by reference into the disclosure of the original patent at Col. 20, line 66 through Col. 21, line 3 by virtue of the phrase "incorporated herein by reference". Incorporations by reference of this type were held proper in, *e.g.*, *Ex parte Maziere*, 27 USPQ2d 1705 (BPAI 1993).

Harrington & Lieber Reference	Amendment
FIG. 1, top structure; FIG. 1 legend, lines 5-6 (oligos SC1/SC3/SC5); sequences of oligos at paragraph bridging pages 4503 and 4504	New FIG. 8 and legend
FIG. 4, 5'-Flap Structure 0 nt gap (lower left); FIG. 4 legend, lines 9-10 (oligos AI4/HJ46/HJ47); sequences of oligos at paragraph bridging pages 4503 and 4504	New FIG. 9A and legend; SEQ ID NO: 64 (AI4); SEQ ID NO: 65 (HJ46)
FIG. 4, 5'-Flap Structure 1 nt gap (lower second from left); FIG. 1 legend, line 10 (oligos AI4/HJ46/HJ73); sequences of oligos at paragraph bridging pages 4503 and 4504	New FIG. 9B and legend; SEQ ID NO: 66 (HJ47)
FIG. 4, 5'-Flap Structure 3 nt gap (lower middle); FIG. 4 legend, line 11 (oligos AI4/HJ46/HJ74); sequences of oligos at paragraph bridging pages 4503 and 4504	New FIG. 9C and legend; SEQ ID NO: 67 (HJ74)
FIG. 4, 5'-Flap Structure 5 nt gap (lower second from right); FIG. 4 legend, lines 11-12 (oligos AI4/HJ46/HJ75); sequences of oligos at paragraph bridging pages 4503 and 4504	New FIG. 9D and legend; SEQ ID NO: 68 (HJ 75)
FIG. 3, Pseudo Y-structure (bottom middle); FIG. 3 legend, line 6 (oligos AI4/HJ46); sequences of oligos at paragraph bridging pages 4503 and 4504	New FIG. 10 and legend
FIG. 5 Panel A, Double Flap #1 (middle, second from right); FIG. 5 legend, line 12 (oligos AI4/HJ46/HJ77); sequences of oligos at paragraph bridging pages 4503 and 4504	New FIG. 11 and legend; SEQ ID NO: 69 (HJ77)
FIG. 5 Panel A, Double Flap #2 (middle right); FIG. 5 legend, line 13 (oligos AI4/HJ46/HJ78); sequences of oligos at paragraph bridging pages 4503 and 4504	New FIG. 12 and legend; SEQ ID NO: 70 (HJ78)
FIGS. 1-6 and respective legends	New FIGS. 13-18 and respective legends
Text beginning at page 4503 "Experimental Procedures" and ending at page 4507, just prior to "Discussion"	Example 4
FIG. 6 legend, lines 6-7; sequences of oligos at paragraph bridging pages 4503 and 4504	SEQ ID NO: 71 (CLH2); SEQ ID NO: 72 (CLH3)
FIG. 6 legend, line 11; sequences of oligos at top of page 4504	SEQ ID NO: 73 (CLH6)

Thus, with the exception of minor confirming changes in the nomenclature of the various flap structures, the brief introduction to Example 4, the incorporation of the full text of the numbered citations directly into the body of the text and the inclusion of the new FIG. references to illustrate the various DNA flap structures,[4/] the added material corresponds to material properly incorporated by reference.

Amendments which replace material incorporated by reference with the actual text of the incorporated document do not constitute new matter. MPEP § 2163.07(b). Since this is all Applicant has done, the amendments do not constitute "new matter" under 35 U.S.C. § 251.

Regarding the rejection of Claims 7-73 for alleged lack of written description, claims added to an application satisfy the written description requirement of 35 U.S.C. § 112 if the disclosure of the application reasonably conveys to a skilled artisan that the inventor, at the time the application was filed, was in possession of the now-claimed subject matter. *Ralston Purina Co. v. Far-Mar-Co.*, 227 USPQ 177, 179 (Fed. Cir. 1985); *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983). The Patent Office alleges Claims 7-73, which are directed to methods, hybridization complexes and kits involving "double flap" structures, have no support in the disclosure of the original patent. Applicant disagrees.

Regarding method Claims 7, 21 and 36, the original disclosure teaches diagnostic methods at Col. 11, lines 3-48 and again at Col. 42, line 63 through Col. 43, lines 36. The methods generally involve contacting a sample believed to contain a target nucleic acid (*see, e.g.*, Col. 42, lines 64-66) with a probe polynucleotide capable of specific hybridization to the target and forming, as a result of such hybridization, a 5'-flap structure which can be cleaved by FEN-1 (*see, e.g.*, Col. 42, line 67 through Col. 43, line 5). A specific embodiment of the methods is illustrated with reference to a particular species of such a 5'-flap structure, the 5'-single flap structure depicted in FIG. 6 (*see, e.g.*, Col. 43, lines 25-29). Additional 5'-single flap structures and another species of such a 5'-flap structure, a 5',3'-double flap structure, are taught in the material incorporated by reference discussed previously (*see, e.g.*, Harrington & Lieber at page 4506). The incorporated material expressly teaches that both 5'-single flap structures and 5',3'-double flap structures are cleavable by FEN-1 (see *id.*).

[4/] These conforming changes are obvious in nature and do not constitute new matter.

Material incorporated into an application or patent disclosure by reference constitutes a part of the original disclosure and may not be ignored in considering whether claims are supported in the manner required by the first paragraph of § 112:

> Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. *The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed.*

MPEP § 2163.07(b) (emphasis added). Thus, the original disclosure, which *includes* the material incorporated by reference, fully supports independent Claims 7, 21 and 36. It teaches the recited methods, the recited cleavable 5',3'-double flap structures and that these structures possess the cleavage characteristics relevant for use in the methods.

Claim 51 recites a hybridization complex comprising a bridge polynucleotide and two polynucleotide probes arranged in a 5',3'-double flap structure. This claim is fully supported by the various 5',3'-double flap structures incorporated into the original disclosure by reference.

Regarding Claim 59, kits for carrying out the various described methods are taught in the original patent at Col. 43, lines 38-52. The kits include a FEN-1 polypeptide having 5'-flap cleavage activity and may be used to practice the diagnostic assays according to the described methods (Col. 43, lines 39-42). From this, skilled artisans would immediately recognize that the kits may include additional reagents for carrying out the methods, such as polynucleotide probes that can be hybridized with a target polynucleotide of interest to create a 5'-flap structure, for example the incorporated 5',3'-double flap structure, that is cleavable by the FEN-1 polypeptide. Skilled artisans would therefore immediately recognize that the original disclosure supports independent Claim 59.

For the convenience of the Patent Office, a table detailing where in the original patent disclosure each of Claims 7-73 finds support is provided below (in the table,"H&L" designates the incorporated Harrington & Lieber article):

Claim	Support: Col. (Lines)
7	11(3-41); 39(65)-40(18); 42(63)-43(36); H&L pp. 4506, Cols. 1 & 2; H&L FIG. 5
21	11(3-41); 39(65)-40(18); 42(63)-43(36); H&L pp. 4506, Cols. 1 & 2; H&L FIG. 5
36	39(65)-40(18); 40(19-34); H&L pp. 4506
8, 9, 34, 35	11(13-17); 43(5-12)
10-13, 26-30, 43-47, 69-73	FIGS. 1-5; 13(19-30)
14, 15, 31, 32, 48, 49, 56, 57, 62, 63	H&L FIG. 5; H&L pp. 4506, Col. 2, lines 3-20
16, 33, 50, 58, 64, 68	19(21-36); FIG. 6
17-19, 22-24, 40-42, 52-54, 60, 65-67	11(24-27); 43(20-22)
20, 25, 38, 55	11(27-28); 43(22-23)
37, 61	40(19-34)
39	H&L pp. 4504, Col. 2, lines 5-17 and 27-39
51	39(65)-40(3); H&L FIG. 5; H&L pp. 4506, Col. 2, lines 3-20
59	43(12-19); 42(63)-43(4); 43(39-53)

This table confirms that the original patent disclosure reasonably conveys to skilled artisans that the inventors were in possession of the inventions recited in Claims 7-73 at the time the original patent application was filed. The first paragraph of 35 U.S.C. § 112 demands no more.

For reasons that are not entirely clear, the Patent Office reproduces paragraphs from the MPEP discussing "essential" and "non-essential" subject matter. Whatever its reasons for doing so, the issue is moot. It simply does not matter whether the material incorporated by reference discussed above is or is not essential to any of Claims 7-73, because, in accordance with common practice, it has been explicitly amended into the instant application . *See* MPEP § 608.01(p)(I)(A)(2).

Accordingly, for the reasons discussed above, Applicant submits none of the subject matter added by amendment is "new" and that Claims 7-73 are fully supported by the disclosure as originally filed. Accordingly, the rejection of Claims 7-73 under 35 U.S.C. §§ 251 and 112, first paragraph, should be withdrawn.

7. REJECTION OF CLAIMS 7-73 UNDER 35 U.S.C. § 251

The Patent Office rejected Claims 7-73 under 35 U.S.C. § 251 as "not being for the same general invention *patented* in the original patent" (Office Action at page 5). Applicant does not understand the rejection. There is no requirement that reissue claims be drawn to the same invention(s) *patented* in the original patent. Section 251 states:

> Whenever any patent is, through error without any deceptive intention, deemed wholly or partly inoperative or invalid, by reason of a defective specification or drawing, or by reason of the patentee claiming more or less than he had a right to claim in the patent, the Director shall, on the surrender of such patent and the payment of the fee required by law, reissue the patent for *the invention disclosed in the original patent*, and in accordance with a new and amended application, for the unexpired part of the term of the original patent. No new matter shall be introduced in to the application for reissue.
>
> * * *
>
> No reissued patent shall be granted enlarging the scope of the claims of the original patent unless applied for within two years from the grant of the original patent.

35 U.S.C. § 251 (emphasis supplied). Controlling case law makes crystal clear that this so-called "original patent" requirement of 35 U.S.C. § 251 does *not* mean that the inventions claimed in the reissue application must have been *claimed* (*i.e.*, patented) in the original patent. *See, e.g., CR Bard Inc. v. M3 Systems Inc.*, 48 USPQ2d 1225, 1234 (Fed. Cir. 1998); *In re Amos*, 21 USPQ2d 1271 (Fed. Cir. 1991). If fact, whether or not the inventions have ever been claimed is completely irrelevant to the essential inquiry under the "original patent" clause of 35 U.S.C. § 251.

In re Amos is illustrative. In *In re Amos*, a reissue applicant attempted to claim an invention that was disclosed, but never claimed, in the original patent. The Patent Office rejected the claims under the "original patent" clause of 35 U.S.C. § 251 on the grounds that

the subject matter of the rejected claims, although disclosed in accordance with 35 U.S.C. § 112, was never claimed in the original patent. On appeal, the Federal Circuit reversed:

> We conclude that, under both *Mead* and *Rowland*, a claim submitted in reissue may be rejected under the "original patent" clause if the original specification demonstrates, to one skill in the art, an absence of disclosure sufficient to indicate that a patentee could have claimed the subject matter.

In re Amos, 21 USPQ2d at 1275 (emphases supplied). Therefore, any inventions that the inventors *could* have claimed in their original application are ripe for claiming in a reissue application, *regardless* of what claims issued in the original patent.

A similar result was reached in *CR Bard*. In *CR Bard*, an accused infringer sought to invalidate claims in a reissue patent drawn to certain biopsy needles under the "original patent" clause of the reissue statute on the grounds that the biopsy needles were never claimed in the original patent or application. Citing *In re Amos*, the Federal Circuit flatly rejected the argument, noting that "a primary purpose of the reissue statute is to enable the addition of claims to subject matter *not claimed in the original patent*." *CR Bard*, 48 USPQ2d at 1234 (emphasis supplied).

The MPEP is consistent with this controlling case law. In discussing the "original patent" requirement of 35 U.S.C. § 251, the MPEP explicitly states:

> The reissue claims must be for the same invention as that *disclosed* as being the invention in the original patent . . . . This does not mean that the invention claimed in the reissue application must have been *claimed* in the original patent . . . .

MPEP § 1412.01 (underlined emphasis in original; italicized emphases supplied).

Furthermore, the extent of amendments made upon filing this reissue application is irrelevant. There is no limit on amendments so long as no new matter is added (see response to new matter rejection, above). Since the instant rejection is based upon an interpretation of the reissue statute that is unsupported by controlling case law (and the MPEP), Applicant submits the rejection of Claims 7-73 under 35 U.S.C. § 251 should be withdrawn.

8. SPECIFICATION

In Claim 14, the word "is" has been deleted from the expression "is comprises" as suggested by the Patent Office. As requested, Applicant will bring to the attention of the

Patent Office any errors in the specification of which Applicant becomes aware during the prosecution of the instant reissue application.

9. REJECTION OF CLAIMS 7-10, 14-27, 31-44 AND 48-70 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Patent Office has rejected Claims 7-10, 14-27, 31-44 and 48-70 under 35 U.S.C. § 112, first paragraph, for lack of written description support in view of *The Regents of the University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). Applicant traverses the rejection.

Regarding rejected Claims 7-10, 14-27, 31-44 and 48-50, *The Regents* is completely inapposite. In *The Regents*, the claims were drawn to compositions of matter, namely, cDNAs encoding vertebrate or mammalian insulins. The claimed CDNAs were defined only by "functional" language that occurred at the exact point of novelty. Under these circumstances, the Court found the written description requirement lacking, because the claimed genuses of cDNAs were distinguishable from other cDNAs only by function:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.*

The Regents, 43 USPQ2d at 1406 (emphases supplied).

Rejected Claims 7-10, 14-27, 31-44 and 48-50 are not drawn to compositions of matter and, in particular, are not drawn to cDNAs encoding a particular protein hormone. Rather, Claims 7-10, 14-27, 31-44 and 48-50 are drawn to *methods* comprising cleavage or binding of double flap structures which have a variety of uses, such as detection of target polynucleotides.

Moreover, functional language has been approved consistently in claims drawn to combinations of elements. *See, e.g, In re Herschler*, 200 USPQ 711 (CCPA 1979); *In re Halleck*, 164 USPQ 647 (CCPA 1970); *In re Fuetterer*, 138 USPQ 217 (CCPA 1963); *In re*

Boller, 141 USPQ 740 (CCPA 1964). For example, in *In re Fuetterer*, a functional description of a genus of salts was held proper in a claim to a composition comprising the salts and other ingredients. *In re Fuetterer*, 138 USPQ at 222 ("inorganic salt that is capable of holding a mixture of said protein and/or carbohydrate in colloidal suspension" upheld in claim to a rubber stock for producing tire treads). In *In re Herschler*, a functional description of a genus of steroids was held proper in a claimed method of enhancing the penetration of a physiologically active steroidal agent across an external barrier membrane of a human or animal subject using an effective amount of DMSO. *The Regents* did not overturn this long-standing precedent.

To the extent *The Regents* is relevant at all, Claims 7-10, 14-27, 31-44 and 48-50 satisfy its holding. Both *The Regents* and the Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1 "Written Description" Requirement[5/] ("Written Description Guidelines") indicate that the written description requirement for a claimed genus may be satisfied in several ways. One acceptable way is through the recitation of a number of representative species falling within the claimed genus. *See* Written Description Guidelines at page 1106, Col. 3, ¶ (2); *The Regents*, 43 USPQ2d at 1406 ("A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus . . . .").

The instant application describes a representative number of species of FEN-1 polypeptides adequate to provide written description support for the genus. For example, the disclosure describes three highly homologous species of FEN-1 polypeptides useful in the claimed methods: human FEN-1 (SEQ ID NO:1), murine FEN-1 (SEQ ID NO:3) and yeast FEN-1 (SEQ ID NO:5) (*see, e.g.*, Col. 13, lines 19-30). A fourth species which has the requisite endonuclease activity, but that differs in some other respects from the three species delineated above, is taught at Col. 54, lines 13-19 (ΔRAD2; SEQ ID NO:7). Additional species of FEN-1 isolated from nuclear extracts of calf thymus, rabbit reticulocytes, Chinese hamster fibroblasts and Drosophila embryos are described at Col. 44, lines 23-27. These species are more than representative of the genus of FEN-1 polypeptides.

[5/] Federal Register 66(4):1099-111 (January 5, 2001).

Accordingly, Applicant submits Claims 7-10, 14-20, 21-27, 31-44 and 48-50 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection as it applies to these claims is therefore requested.

Regarding Claims 51-58 the Patent Office suggests the claimed hybridization complexes are defined only by functional language, presumably because the primary nucleotide sequences of the polynucleotide probes and target nucleic acid are not specified. This is simply not the case. Both *The Regents* and the Written Description Guidelines indicate that another way to satisfy the written description requirement for a claimed genus is by disclosure of relevant identifying characteristics, *e.g*, structure or other physical and/or chemical properties sufficient to distinguish the claimed subject matter from other materials. *The Regents*, 43 USPQ2d at 1406; Written Description Guidelines at page 1106, Col. 3, ¶(2). There is no requirement that the relevant identifying characteristics of polynucleotides such as the claimed hybridization complexes be limited to their primary nucleotide sequences. *Any* relevant identifying characteristics are sufficient.

The hybridization complexes recited in rejected Claims 51-58 are described by appropriate relevant identifying characteristics. Namely, the hybridization complexes of Claims 51-58 comprise a bridge polynucleotide, a first polynucleotide probe and a second polynucleotide probe that, as recited in the "wherein" clause, specifically hybridize to one another to yield a double flap structure. This structure can be readily distinguished from other structures, such as, for example, 5'-overhangs, 3'-overhangs, pseudo-Y structures. Accordingly, Claims 51-58 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

Kit Claims 59-70 likewise satisfy the written description requirement. Independent Claim 59 recites a kit for detecting the presence of a target nucleic acid comprising a FEN-1 polypeptide, a first polynucleotide probe, and a second polynucleotide probe, wherein the first and second probes are capable of forming a hybridization complex of the type recited in Claim 51. In such a claimed combination, recitation of a FEN-1 polypeptide without more is proper in light of the discussion above.

Accordingly, since Claims 59-70 satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, withdrawal of the rejection is requested.

10. REJECTION OF CLAIMS 51-58 UNDER 35 U.S.C. § 101

Claims 51-58 stand rejected under 35 U.S.C. § 101 for lack of utility. The rejection is respectfully traversed.

Pursuant to the Utility Examination Guidelines[6/] ("Utility Guidelines"), in order to satisfy the utility requirement 35 U.S.C. § 101, an application need only disclose or make apparent one specific and substantial utility for each invention claimed (*see, e.g.,* Utility Guidelines at pages 1097-98). Several utilities are apparent for the hybridization complexes of Claims 51-58, including, for example, detecting target nucleic acids (*e.g.*, Col. 42, line 63 through Col. 43, line 36) and purifying or detecting enzymes with activity towards the recited complexes (*e.g.*, Col. 19, lines 8-20, keeping in mind Col. 39, line 65 through Col. 40, line 3). Any one of these utilities is sufficient to satisfy the requirements of 35 U.S.C. § 101. Accordingly, the rejection should be withdrawn.

Claims 51-58 have also been rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for reasons flowing from the alleged lack of utility. Since Applicant has established that the claimed hybridization complexes have a utility, the related rejection under 35 U.S.C. § 112, first paragraph, is moot. Accordingly, the rejection of Claims 51-58 under 35 U.S.C. § 112, first paragraph, should be withdrawn as well.

11. REJECTION OF CLAIMS 7-73 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 7-73 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement due to the failure to include specific hybridization conditions in the claims. Applicant traverses the rejection.

The test for enablement is whether one skilled in the art can make and use the claimed invention without undue experimentation. *See, e.g.*, MPEP § 2164.01; *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). The enablement requirement can be satisfied even though some experimentation may be required. *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81 (Fed. Cir. 1986).

This instant application provide ample guidance regarding conditions for carrying out the various claimed inventions. Suitable conditions for practicing the claimed methods, hybridization complexes and kits are taught, for example, at Col. 39, line 65 through Col. 40,

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[6/] Federal Register 66(4):1092-99 (January 5, 2001).

line 18. Additional conditions are taught in the various material incorporated by reference at Col. 39, line 65 through Col. 40, line 3. For example, as evidenced in the respective articles, the binding and cleavage reaction conditions incorporated from Harrington & Leiber, 1994, *EMBO J.* 13(5):1235-46 and Harrington & Lieber, 1994, *Gene & Development* 8(11):1344-55 are suitable for practicing the claimed inventions. Additional conditions for carrying out hybridizations and cleavage are taught in the working examples at, for example, Col. 49, line 51 through Col. 52.

Moreover, as explicitly taught in the original disclosure, the actual conditions are not critical for success, and various modifications may be made. *See, e.g.*, Col. 40, lines 9-18. Guidelines for determining which modifications are suitable are provided at Col. 40, lines 13-18.

Furthermore, the art of nucleic acid hybridizations was extremely well developed at the time the original patent application was filed. Several standard laboratory manuals describing the various principles underlying nucleic acid hybridizations and providing myriad conditions for carrying out hybridizations were available to skilled practitioners. Two specific examples are the Sambrook *et al.* molecular cloning laboratory manual incorporated by reference at Col. 20, lines 47-51 and *Nucleic Acid Hybridization: A Practical Approach*, Hames & Higgins, eds, IRL Press, Oxford, England, 1988. As evidenced by these manuals, at the time the application was filed, ordinarily skilled practitioners routinely engaged in selecting hybridization conditions suitable for particular applications.

Accordingly, from the teachings in Applicant's disclosure, combined with the knowlege available in the art, ordinarily skilled practitioners would have had no difficulty in making operative the inventions as claimed. Accordingly, the enablement requirement is satisfied and the rejection should be withdrawn.

12. REJECTION OF CLAIM 7 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 7 stands rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential elements. The Patent Office alleges that cleavage, release, incubation, detection and quantification steps are missing. The rejection is in part moot in light of the amendment of Claim 7 and in part traversed.

Regarding the detection and quantification steps, Applicant notes that Claim 7 has been amended to add a step (c), which now recites detecting or quantifying the cleavage. As noted in the original patent at Col. 11, lines 11-17, cleavage can be detected and optionally quantified. Accordingly, both steps are not required and it is proper to recite "detecting" and "quantifying" in the alternative.

Applicant submits no other steps have been omitted. Step (b) of amended Claim 7 recites "selectively cleaving" the polynucleotide to release a nucleotide or a polynucleotide from its 5'-region. This step subsumes the cleavage, release and incubation steps the Patent Office believes are omitted. While the disclosure at Col. 11, line 11 recites "incubating with FEN-1," when read in the context of the complete disclosure, skilled artisans would immediately recognize that this passage supports step (b) as presently drafted. Specifically, the definition of FEN-1 makes it clear that this expression is generic in scope. The entire disclosure teaches that FEN-1 is an endonuclease capable of specifically cleaving certain polynucleotides. Applicant reminds the Patent Office that the claimed subject matter need not be described *in haec verba* to satisfy the written description requirement. *In re Herschler*, 200 USPQ 711, 717 (CCPA 1979). The disclosure need describe the claim limitations only so clearly that one having ordinary skill in the art would recognize that the inventors invented the method including the claimed limitations. *Id.* This requirement has been met.

Accordingly, Applicant submits no essential elements of amended Claim 7 are omitted, and that amended Claim 7 satisfies the second paragraph of Section 112. Applicant therefore requests that the rejection be withdrawn.

13. REJECTION OF CLAIMS 1, 4 AND 5 UNDER 35 U.S.C. § 102(a)

Claims 1, 4 and 5 stand rejected under 35 U.S.C. § 102(a) as being allegedly anticipated by Murray *et al.*, July 1994, *Mol. Cell Biol.* 14(7):4878-4888 ("Murray *et al.*"). Applicant traverses the rejection.

For a prior art reference to anticipate a claim under Section 102, every element of the claimed invention must be identically taught in the reference. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990). According to the Patent Office, Murray *et al.* anticipates Claims 1, 4 and 5 because a fragment which is not size-limited will inherently have activity. Independent Claim 1, from which Claims 4 and 5 depend, recites an isolated polynucleotide encoding a

FEN-1 polypeptide as shown in SEQ ID NO:1 or SEQ ID NO:3, or a *fragment of said polypeptide having endonucleolytic cleavage activity*. Applicant submits the language "fragment of said polypeptide" indeed includes a size limitation. By its plain language, the fragment must be shorter in length than the polypeptides of SEQ ID NOS:1 & 3. The Murray *et al.* reference teaches only the full-length hRAD2 protein and a polynucleotide encoding the full-length protein. It does not teach or suggest any hRAD2 fragments having endonucleolytic activity or polynucleotides encoding such fragments, as recited in Claim 1. As a consequence, Murray *et al.* does not anticipate Claim 1, or Claims 4 and 5 which depend therefrom. Removal of the rejection is therefore requested

14. REJECTION OF CLAIMS 7-9 AND 51 UNDER 35 U.S.C. § 102(b)

Claims 7-9 and 51 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Lyamichev *et al.*, 1993, *Science* 260:778-783 ("Lyamichev *et al.*"). Applicant traverses the rejection on the grounds that the Lyamichev *et al.* reference does not identically teach the method of Claims 7-9 or the hybridization complex of Claim 51.

Lyamichev *et al.* teach the cleavage of certain polynucleotide structures with DNA polymerases ("DNAPs"). In Fig. 1, the authors demonstrate that DNAP from *Thermus aquaticus* ("DNA-Taq") cleaves a polynucleotide having a 5'-single strand flap structure. In contrast, method Claims 7-9 involve cleaving a hybridization complex comprising a target polynucleotide, a 5'-polynucleotide probe and a 3'-polynucleotide probe that, by virtue of the recited arrangement of the probes in the hybridization complex, has a double-flap structure (examples of which are illustrated in FIGs. 11 & 12 of the instant application). Similarly, Claim 51 recites a hybridization complex having a double-flap structure. Since Lyamichev *et al.* does not teach or suggest polynucleotides having double-flap structures, it does not anticipate Claims 7-9 and 51. Applicant therefore requests withdrawal of the rejection.

15. REJECTION OF CLAIMS 7-73 UNDER 35 U.S.C. § 103(a)

Claims 7-73 stand rejected under 35 U.S.C. § 103(a) as being obvious over Harrington & Lieber, 1994, *EMBO Journal* 13(5):1235-1246 ("Harrington & Lieber II). Applicant traverses the rejection on the ground that the Patent Office has failed to establish a *prima facie* case of obviousness.

When rejecting claims under 35 U.S.C. § 103(a), the Patent Office bears the burden of establishing a *prima facie* conclusion of obviousness. In order to do so, the Patent must demonstrate three elements: (1) that the prior art provides a suggestion or motivation to modify or combine the teachings of the references relied upon by the Office to reject the claims; (2) that the prior art provides one of skill in the art with a reasonable expectation that the suggested combination or modification would be successful; and (3) that the prior art, either alone or in combination, teaches each and every limitation of the rejected claims. The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not in applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). See also, *WMS Gaming Inc. v. Int'l. Game Technology*, 51 USPQ2d 1385, (Fed. Cir. 1999). These three elements are distinct. If any one is not established, *prima facie* obviousness is not established, and Applicant is *not* required to show indicia of unobviousness, such as new or unanticipated results. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

The cited Harrington & Lieber II article fails to render amended Claims 7-73 *prima facie* obvious. In particular, the Harrington & Lieber II article does not teach or suggest double-flap structures. Each of independent Claims 7, 21 and 36 recites a method involving cleavage of a double-flap structure. Likewise, independent Claim 51 recites a hybridization complex having double-flap structure and independent Claim 59 recites a kit for detecting the presence of a target nucleic acid comprising, *inter alia*, probes capable of hybridizing with the target so as to form a double-flap structure. All of the remaining claims ultimately depend from these independent claims. Since the cited Harrington & Lieber II article fails to teach or suggest double-flap structures, or provide any reasonable expectation that such structures could be cleaved, it does not render Claims 7-73 obvious. Accordingly, Applicant requests that the rejection of Claims 7-73 under 35 U.S.C. § 103(a) be withdrawn.

16. CONCLUSION

For the reasons discussed above, Claims 7-73 satisfy all requirements for patentability and are in condition for allowance. An early notification of the same is therefore kindly requested.

If the Examiner determines that prosecution of the instant application would benefit from a telephonic interview, the Examiner is invited to call the undersigned attorney.

No fees are believed due in connection with this response. However, the Patent Office is authorized to change any deficient or required fees, or to credit any over payment, to Pennie & Edmonds, LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date June 15, '01

Samuel B. Abrams 30,605 (Reg. No.)

Enclosures

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EXHIBIT A

Marked-Up Copy of Amended Claims

7. (Amended) A method of cleaving a polynucleotide, comprising the steps of:

(a) contacting a sample suspected of containing a target nucleic acid of interest, said target nucleic acid comprising a first portion and a second portion located immediately 3' to the first portion, with:

(i) a 5'-polynucleotide probe comprising a 3'-region that is capable of specifically hybridizing to the first portion of the target nucleic acid and a 5'-region located immediately 5' to the 3'-region; and

(ii) a 3'-polynucleotide probe comprising a 5'-region that is capable of specifically hybridizing to the second portion of the target nucleic acid and a 3'-region located immediately 3' to the 5'-region,

under conditions in which the 3'-region of the 5'-probe and the 5'-region of the 3'-probe specifically hybridize immediately contiguously with one another to the first and second portions, respectively, of the same target nucleic acid molecule; [and]

(b) selectively cleaving the 5'-polynucleotide probe to release a nucleotide or a polynucleotide from its 5'-region; and

(c) detecting or quantifying said cleavage.

8. (Amended) The method of Claim 7 [further including the step of] in which step (c) comprises detecting the presence of the released nucleotide or polynucleotide, where the presence of the released nucleotide or polynucleotide correlates with the presence of the target nucleic acid in the sample.

9. (Amended) The method of Claim 7 [further including the step of] in which step (c) comprises quantifying the amount of nucleotide or polynucleotide released, where the quantity of released nucleotide or polynucleotide correlates with the presence or abundance of the target nucleic acid in the sample.

14. (Amended) The method of Claim 7 in which the 3'-probe [is] comprises a 3'-flap region that is 1 to 10 nucleotides in length.

51. (Amended) A hybridization complex comprising:

(a) a bridge polynucleotide comprising a first portion and second portion located immediately 3' to the first portion;

(b) a first polynucleotide probe comprising a 3'-region and a 5'-region located immediately 5' to the 3'-region; and

(c) a second polynucleotide probe comprising a 5'-region and a 3'-region located immediately 3' to the 5'-region,

wherein the 3'-region of the [5'-probe] first probe and the 5'-region of the [3'-probe] second probe are specifically hybridized immediately contiguously with one another to the first and second portions, respectively, of the same bridge polynucleotide molecule, thereby forming a hybridization complex.

59. (Amended) A kit for detecting the presence of a target nucleic acid in a sample, comprising:

(a) a FEN-1 polypeptide;

(b) a first polynucleotide probe comprising a 3'-region capable of specifically hybridizing to a first portion of a target nucleic acid of interest and a 5'-region located immediately 5' to the 3'-region; and

(c) a second polynucleotide probe comprising a 5'-region capable of specifically hybridizing to a second portion of the target nucleic acid which is located immediately 3' to the first portion and a 3'-region located immediately 3' to the 5'-region,

wherein the 3'-region of the [5'-probe] first probe and the 5'-region of the [3'-probe] second probe are capable of specifically hybridizing immediately contiguously with one another to the first and second portions, respectively, of the same target nucleic acid molecule to form a structure that is capable of being bound or cleaved by the FEN-1 polypeptide.